REMARKS

I. Support for the Amendments

Support for the amendment to the specification can be found in the parent application and in the Initial Information Data Sheet filed concurrently with the present application on February 1, 2001.

Claims 1-21 were originally in the application. Claims 1-5 were canceled previously without prejudice or disclaimer of any subject matter. Claims 6-31 were previously in the application.

Claims 6-32 are presently in the application. Claims 7 and 24-26 have been amended, and new claims 32-34 have been added. No new matter has been added by virtue of this amendment.

The amendment to claim 7 is technical in nature and reinstates the claim number of the dependency, which was inadvertently omitted during a previous amendment. Support for this amendment can be found in claim 7 as originally filed.

The amendments to claims 24-26 are technical in nature and reflect the changed numbering of the figure from Figures 3A-3B (informal drawing) to Figures 3A-3D (formal drawing). Support for this amendment can be found in Figures 3A-3B as filed.

Support for new claims 32-34 can be found in the original specification and claims. Additional support for claims 32-33 can be found, e.g., on page 6, lines 10-14; and in the Examples and Figures. Additional support for claim 34 can be found, e.g., on page 3, lines 2-22; on page 4, lines 1-4; on page 5, line 25; on page 6, lines 1-7; on page 7, lines 4-10 and 24-25; from page 8, line 25, to page 11, line 4; from page 12, line 10, to page 13, line 2; on page 13, lines 11-18; and in the Examples, particularly in Examples 1-3, and Figures.

II. Status of the Claims

Claims 1-21 were originally in the application. The present application is a divisional application resulting from a restriction requirement. Claims 1-5 were canceled without prejudice or disclaimer of any subject matter. Claims 6-31 were previously in the application.

Claims 6-34 are presently in the application. Claims 7 and 24-26 have been amended, and new claims 32-34 have been added. No new matter has been added by virtue of this amendment.

III. The Information Disclosure Statements

Applicants respectfully request the Examiner to acknowledge the Information Disclosure Statement, mailed on February 1, 2001, and the references cited therein. Applicants thank the Examiner for acknowledging the Information Disclosure Statement, mailed on March 8, 2005, and the references cited therein.

IV. The Request to Update the Specification is Accommodated

The Examiner has requested Applicants to update the status of all U.S. application disclosed in the specification. Applicants have amended the cross-references to related applications accordingly. Support for the amendment to the specification can be found in the parent application and in the Initial Information Data Sheet filed concurrently with the present application on February 1, 2001.

V. Rejection of Claims 6, 9-12, 15-19, and 22-30 Under 35 U.S.C. §112, First Paragraph, with Respect to the Written Description, is Traversed

The Examiner has rejected claims 6, 9-12, 15-19, and 22-30 under 35 U.S.C. §112, first paragraph, "as failing to comply with the written description requirement." Applicants respectfully traverse the Examiner's rejection.

The Patent Office alleges in part:

> There is no support in the specification as originally filed for the recitation of "transmembrane and cytoplasmic region of a CD3, CD8 or CD16 receptor" in claim 6 or 11 or 18. Regarding applicants comments, the cited passage of the specification discloses use of zeta regions of the CD3, CD8 or CD16 receptor, but does not disclose the scope of the claimed invention which encompasses use of portions of said molecules other than the zeta region. [P. 2, par. 5.]

Applicants respectfully disagree. Regarding the support for the "transmembrane and cytoplasmic region" language, Applicants respectfully submit that the specification as filed does indicate that regions other than the zeta regions could be used:

> It is important to recognize that the critical feature of the nucleic acid encoding the TCR derivative is the presence of the variable regions from the α and β chains, and that **additional sequence, perhaps for added stability, including some or all of the constant region may be present**. In addition, **alternative transmembrane and signalling regions other than the regions other than the ζ regions exemplified above may be substituted**. Thus, the recombinant materials encoding the TAA-specific, human MHC restricted TCR derivatives of the invention need only include the variable a and P regions of the relevant TCR **along with some additional transmembrane and signalling sequence and may further include additional non-interfering amino acid sequence**. [P. 6, ll. 19-27; all emphasis added.]

Claims 9-12, 15-19, and 22-30 are dependent on claim 6, and the same arguments also apply to these claims.

In addition, the Patent Office alleges:

> There is no support in the specification as originally filed for the scope of claims 24-28. Applicant has indicated that said claims find support in Figure 1. Regarding claim 24, Figure 1 discloses a variety of specific constructs. However, the claimed nucleic acid encompasses constructs not depicted in said Figure. The claimed nucleic is broader in scope than said disclosure because it lacks the leader sequence, it doesn't specify that the variable region is attached to the transmembrane portion of the zeta chain, and it encompasses other attached molecules or amino acids because of the use of comprising language. Regarding claim 25, the claimed nucleic is broader in scope than said disclosure because it lacks the leader sequence, it doesn't specify that the variable region is attached to the transmembrane portion of the zeta chain, and it encompasses other attached molecules or amino acids because of the use of comprising language. Regarding claim 26, Figure 1 shows a CD8 hinge inserted into a particular region of the construct whilst the claim encompasses a CD 8 hinge that is inserted other than in said location. [Pp. 2-3, par. 5.]

Applicants respectfully disagree. Regarding the rejection of claims 24-28, Applicants respectfully submit that these claims are supported by Figure 3 and language elsewhere in the specification. Indeed, claims 24-26 specifically cite Figures 3A-D (formerly Figures 3A-B). In the passage quoted above (p. 6, ll. 19-27), Applicants also indicate that the critical features of the nucleic acid is the TCR variable regions and that other non-interfering sequences can be included. Thus, the claimed nucleic acids are not beyond the scope of the disclosure.

Moreover, to limit the claims to specific links or insertion sites would unduly limit the scope of the claims. One of ordinary skill in the art would recognize that polynucleotides can include a wide range of linkers without affecting the activity of the resulting fusion protein. An example of this type of polynucleotide would be a protein expression vector. Other examples are well-known to those of skill in the art. Similarly, one of skill in the art would recognize that the positioning of the hinge region need not be restricted to a specific location.

Claim 26 is dependent on claim 24 or claim 25, claim 27 is dependent on claim 26, and claim 28 is dependent on claim 6, so the arguments above apply to these claims as well.

Applicants respectfully submit that the present claims 6, 9-12, 15-19, and 22-30 fulfill the requirements of 35 U.S.C. §112, first paragraph, with respect to the written description and request the Examiner's reconsideration of these claims accordingly.

VI. Rejection of Claims 6-10, 15-19, 23, and 28-31 Under 35 U.S.C. §103 over Mule in view of Sette is Traversed

The Examiner has rejected claims 6-10, 15-19, 23, and 28-31 under 35 U.S.C. §103(a) as being unpatentable for obviousness over Mule (WO 97/06409) in view of Sette et al. (FASEB J. 9: A801 (April 1995); "Sette"). Applicants respectfully traverse the Examiner's rejection.

The Patent Office alleges:

> Mule teaches a nucleic acid encoding a TCR alpha and beta chain which binds a tumor antigen wherein the construct also includes the c region of CD3 (see claims 1-3,8,13, page 16, penultimate paragraph) wherein claim 8 encompasses the molecule of claim 2. Mule teach expression vectors encoding nucleic acids comprising a leader sequence and said TCR, and T cells containing said vectors and methods of making the aformentioned (see page 14-16). Human CD3 is known in the art. Mule teaches single chain TCR (see page 15, second paragraph). Mule does not teach use of a nonhuman TCR which is HLA A2 restricted. Mule discloses that the TCR can be derived from known CTL (see page 15, second paragraph). Sette et al. disclose the use of HLA A2 transgenic mice that produce T cells with nonhuman TCR that are HLA A2 restricted (see page 5588, second column). Said system has the advantage that T cells can be produced by immunizing mice using methods not acceptable in humans (for example immunization of antigen with IFA used in the example, page 5587, second column). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Mule teaches the claimed invention except for use of nonhuman TCR, whilst methods of generating nonhuman TCR that were HLA A2 restricted were known in the art. One of ordinary skill in the art would have been motivated to do the aformentioned because Mule discloses that the TCR can be derived from known CTL. [P. 4, par. 7.]

Applicants respectfully disagree and traverse this rejection.

Mule has been discussed previously (e.g., Amendment mailed December 19, 2002), and the previous remarks apply here also. In addition, Mule is directed to DNA molecules encoding an antigenic specificity region and a signal-transducing region. In one embodiment referred to as a "chimeric TCR", the signal-transducing region is obtained from a T cell specific receptor or the Fcγ receptor and the antigenic specificity region is obtained from an immunoglobulin. The

Patent Office states that the "chimeric" constructs of claim 8 and 13 of Mule anticipate Applicants' claimed constructs. However, Mule's "chimeric" constructs clearly refer to molecules containing antibody-derived antigen binding domains (see Mule, e.g., page 7 lines 8-11, page 15, lines 11-15, page 15, line 28 to page 16 line 7). Mule neither teaches nor suggests chimeric constructs comprising a variable region of a TCR and the transmembrane/cytoplasmic region of the CD3, CD8 or CD16 receptor, nor does Mule suggest that such a construct is desirable.

In a different embodiment referred to as a recombinant TCR or "classic TCR", the antigenic specificity region and signal-transducing region are both obtained from TCRs or full-length TCR chains (see Mule, e.g., page 7, line 7-8; page 15 lines 8-27). Mule's description of the classic TCR constructs does not teach or suggest the constructs encoding TCR α or β polypeptide fused to the transmembrane/cytoplasmic region of the CD3, CD8 or CD16 receptor. Nothing in Mule teaches or suggests that a functional molecule could be produced by combining the antigen recognition domain of a TCR with the signal transducing region of the CD3, CD8 of CD16 receptor. Mule does not teach or suggest use of a non-human TCR which is HLA-A2 restricted, nor does Mule suggest that such a construct is desirable.

Sette does not remedy the deficiencies of Mule. Sette describes the use of HLA-A*0201/Kb transgenic mice that, in response to immunization with viral peptides, produce T cells with nonhuman TCR that are A*0201/Kb-restricted. However, Sette does not teach or suggest use of the T cells to generate a nucleic acid molecule of claim 6 of the current application. In addition, Sette does not teach or suggest generation of T cells with non-human TCR specific for a tumor-associated antigen. In fact, Sette teaches that the properties of the peptides inducing a T cell response in the HLA-A*0201/Kb transgenic mice may differ from those identified as immunodominant in humans (e.g., p. 5590, Table IV). Thus, it would be difficult to extrapolate from the results shown in Sette for viral peptides to other antigens including those identified from human tumors.

The combined teachings of Mule and Sette do not disclose the nucleic acid molecule of claim 6 of the current application. Moreover, there is no motivation to combine the teachings of Mule with those of Sette in the first instance.

Claims 7-10, 15-19, 23, and 28-31 are directly or indirectly dependent on claim 6, and the same arguments also apply to these claims.

Applicants respectfully submit that the present claims 6-10, 15-19, 23, and 28-31 fulfill the requirements of 35 U.S.C. §103(a) and request the Examiner's reconsideration of these claims accordingly.

VII. Rejection of Claims 11-14 Under 35 U.S.C. §103 over Mule in view of Sette and further in view of Reinherz is Traversed

The Examiner has rejected claims 11-14 under 35 U.S.C. §103(a) as being unpatentable for obviousness over Mule (WO 97/06409) in view of Sette et al. (FASEB J. 9: A801 (April 1995); "Sette") and further in view of Reinherz et al. (U.S. Patent 6,416,971; "Reinherz"). Applicants respectfully traverse the Examiner's rejection.

The Patent Office alleges:

> The previous rejection renders obvious the claimed invention except for use of a flexible linker such as that of claim 12. Reinherz et al. teaches a flexible linker encompassed by that recited in claim 12 and the advantages of using such a linker to connect the alpha and beta chains of a TCR construct (see column 4, penultimate paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Mule teaches the claimed invention except for use of a flexible linker such as that of claim 12 whilst Reinherz et al. teaches a flexible linker encompassed by that recited in claim 12 and the advantages of using such a linker to connect the alpha and beta chains of a TCR construct. [Pp. 4-5; par. 8.]

Applicants respectfully disagree and traverse this rejection accordingly. Applicants respectfully request additional clarification with respect to claim 12.

Both Mule and Sette have been discussed at length, *supra*, and the same remarks apply here. Reinherz fails to supply for the deficiencies of Mule and Sette, either alone or in combination.

Reinherz has been discussed previously (e.g., Amendment mailed December 19, 2002), and the previous remarks apply here also. In particular, **Reinharz as cited does not teach or suggest any single chain and non-human TCR that is human HLA restricted**. Further, **the Reinharz patent as relied on does not teach or suggest making any** non-human and human HLA-restricted **TCR in which the single chain is coupled to a portion of any CD3, CD8 or CD16 receptor**. Reinherz neither teaches nor suggests the benefits of having Applicants' non-human TCR restricted to human HLA has already been discussed. Further, Applicants found that by coupling a transmembrane and cytoplasmic part of the CD3, CD8, or CD16 receptor to the non-human TCR encoded by the claimed nucleic acid, it was possible to assist in producing stable TCR molecules and avoid competition for dimerization with endogenous TCR.

The Patent Office relies on Reinherz to teach the flexible linker to connect the alpha and beta chains of the TCR construct of claim 12 of the current application. However, Reinherz teaches a single-chain T-cell receptor construct with the requirement that the resulting TCR molecule be soluble (see, e.g., column 4, lines 18-20; Abstract; column 2, lines 18-24; claim 1). Specifically, Reinherz discloses that any portions of the TCR subunits may be employed as long as the portions used lack the transmembrane region (e.g., column 3, lines 62-64) and that the linker permit joining of the subunits to form the antigen binding site and preferably impart aqueous solubility to the molecule (e.g., column 4, lines 30-34). In contrast to Reinherz, the constructs of the current application encode TCR molecules comprising a transmembrane region. The resulting TCRs are not soluble but are associated with the cell membranes. Given the structural and solubility differences between the TCR constructs of Reinherz and the current

application it would not be prima facie obvious to one of ordinary skill in the art to use the linker of Reinherz for the soluble single chain TCR molecules for the constructs disclosed in claims 11-14. Reinherz neither teaches nor suggests the present invention.

Moreover, as discussed *supra*, there is no motivation to combine the teachings of Mule and Sette, and there is no motivation to combine them with Reinherz.

Claims 12-14 are directly or indirectly dependent on claim 11, and the same arguments apply with respect to those claims.

Applicants respectfully submit that the present claims 11-14 fulfill the requirements of 35 U.S.C. §103(a) and request the Examiner's reconsideration of these claims accordingly.

VIII. Rejection of Claims 22 Under 35 U.S.C. §103 over Mule in view of Sette and further in view of Disis is Traversed

The Examiner has rejected claims 22 under 35 U.S.C. §103(a) as being unpatentable for obviousness over Mule (WO 97/06409) in view of Sette et al. (FASEB J. 9: A801 (April 1995); "Sette") and further in view of Disis et al. ("Disis"). Applicants respectfully traverse the Examiner's rejection. Applicants wish to go on record that the citation for the Disis reference was not provided and that they were unable to obtain a response from the Patent Office to their requests for clarification prior to the deadline.

The Patent Office alleges:

> The previous rejection renders obvious the claimed invention except wherein the tumor associated antigen is Her2/neu. Mule teaches that the TCR used can recognize cancer cells (see page 16, penultimate paragraph). Disis et al. teach that HER-2/neu is a cancer cell antigen recognized by T cells. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the previous rejection renders obvious the claimed invention except wherein the tumor associated antigen is Her2/neu, Mule teaches that the TCR used can

recognize cancer cells whilst Disis et al. teach that HER-2/neu is a cancer cell antigen recognized by T cells. [P. 5, par. 9.]

Applicants respectfully disagree and traverse this rejection accordingly.

Both Mule and Sette have been discussed at length, *supra*, and the same remarks apply here. Disis fails to supply for the deficiencies of Mule and Sette, either alone or in combination.

Applicants assume that the Disis reference is Cancer Research 54:1071-1076 (1994). Disis identifies the HER-2/neu antigens by in vitro immunization in a culture system using human peripheral blood lymphocytes. This method is quite different from immunizing HLA-A2 mice and analyzing peptide-specific mouse CTLs. Sette shows that viral antigens recognized by human CTLs can differ from those immunogenic in immunized HLA-A2 mice. So the methods of Disis are not instructive for selecting HER-2/neu antigens immunogenic in the non-human animal. Disis is also silent on other tumor antigens listed in the current application.

For example, while Disis describes HER-2/Neu as an oncogene and outlines tumor associated antigens of HER-2/neu that elecit peptide-specific CTL responses from human peripheral blood lymphoctes, the candidate TAAs defined in Disis as showing specific lytic activity after the tenth in vitro stimulation and also showing greater lytic activity and peptide specificity after multiple restimulation (p48-56 and p789-797 in Table 2 on page 1073; see also Fig. 1) do not all elicit significant CTL responses in HLA transgenic animals (H12 and H16 in Table 1 of the present application). Again, these findings again indicate that, as discussed for Sette, results in other systems do not necessarily correspond to results in the system of the present invention.

Applicants respectfully submit that the present claim 22 fulfills the requirements of 35 U.S.C. §103(a) and request the Examiner's reconsideration of this claim accordingly.

CONCLUSION

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Applicants believe that a one-month extension of time is required and submit the appropriate fee herewith. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time. Although it is not believed that any fee is required, in addition to the fee submitted herewith, to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

Date: February 13, 2006

Kathryn A. Piffat, Ph.D. (Reg. No. 34,901)
EDWARDS & ANGELL, LLP
P. O. Box 55874
Boston, MA 02205
Tel. (617) 439-4444
Fax (617) 439-4170

Customer No. 21874